
1.2. THYROID AND PARATHYROID PHYSIOLOGY

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The purpose of this chapter is to review the details of thyroid anatomy and physiology that facilitate an understanding of thyroid cancer management.

EMBRYOLOGY

The thyroid is embryologically derived from the primitive foregut and neural crest cells. The gland is comprised of two types of secretory cells: follicular cells that arise from the embryonic foregut and C cells that are derived from the neural crest (Santisteban 2005). These two cell types, respectively, synthesize thyroid hormone and calcitonin, the two main classes of hormones in the gland. The functional subunits of the thyroid are sphere-shaped follicles that contain an intra-luminal pool of colloid. Cuboidal follicular cells that synthesize and secrete thyroid hormones make up the lining of each follicle (Fig. 1). A thin layer of connective tissue containing a dense network of capillary and lymphatic vessels separates the follicles from each other. Within the interfollicular connective tissue, and interspersed among the follicular cells, are the thyroidal C cells that synthesize calcitonin.

THYROID HORMONE

The thyroid gland produces two biologically active forms of thyroid hormone: thyroxine (3, 5, 3', 5' iodothyronine or T₄) and triiodothyronine (3, 5, 3' iodothyronine or T₃) (Engler 1984). Both contain an outer phenyl ring and an inner tyrosine ring attached by an ether linkage (Fig. 2). Conceptually it is useful to think of T₄ as the

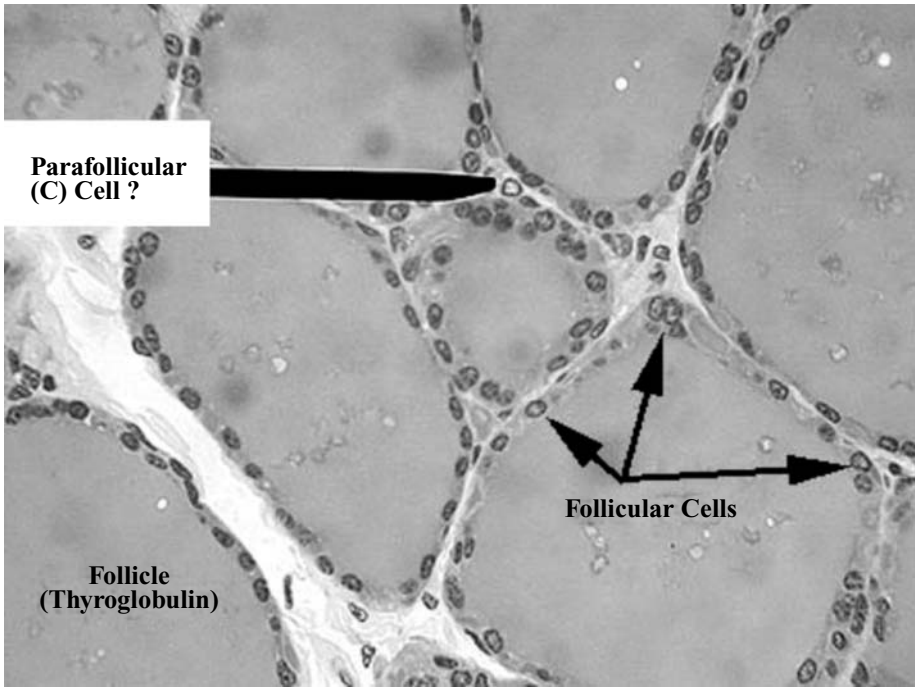


Figure 1. Thyroid follicle. Thyroid follicular cells produce thyroglobulin and thyroid hormone. Thyroid C cells, synthesize and secrete calcitonin.

storage and transport form of thyroid hormone and T3 as the metabolically active form. Most (~80%) thyroid hormone in the thyroid gland and plasma is T4, which is rapidly converted to T3 in skeletal muscle, liver, brain and other tissues by removal of an outer ring 5' iodine molecule. T3, and to a much smaller extent T4 (which acts mainly as a prohormone), are bound to specific nuclear receptors in peripheral cells that interact with regulatory regions of genes, influencing their expression. The tissue concentration of T3 almost completely determines the biologic effect of thyroid hormone. Levothyroxine (T4) alone is effective thyroid hormone replacement therapy because T3 is almost exclusively derived from T4.

IODINE AND THYROID FUNCTION

Iodine is essential for normal thyroid function (Fig. 2). The minimum daily intake necessary to prevent iodine deficiency goiter is 50 μg and the recommended daily intake is 150 μg . Urinary iodine is a reflection of iodine intake. Urinary iodine level was about 600 to 700 $\mu\text{g/L}$ per day in the U.S. a few years ago but has been falling in recent years and now averages only about 150 $\mu\text{g/L}$ (Hollowell 1998; Hollowell 2002).

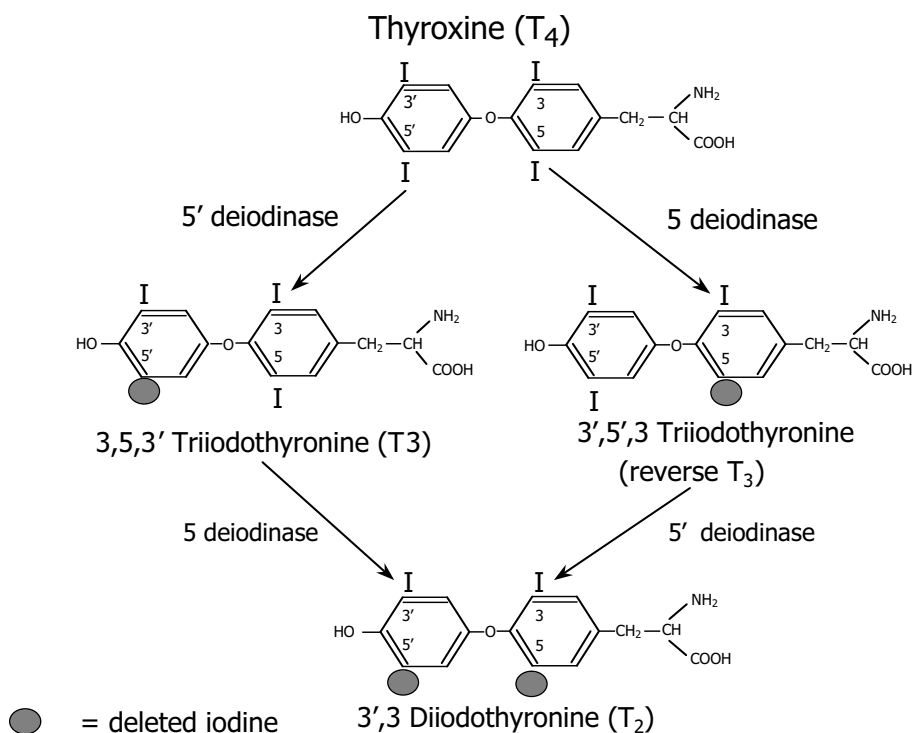


Figure 2. The normal thyroid produces 80 to 100 μg of T₄ per day. About 10% of T₄ is degraded each day and about 80% is deiodinated, 40% to form T₃ and 40% to form rT₃ and the remaining 20% is conjugated with glucuronide and sulfate, deaminated and decarboxylated to form tetraiodothyroacetic acid (tetrac) or the two rings are cleaved. About 80% of the T₃ is formed by 5'-deiodination (outer ring) of T₄ in extrathyroidal tissue. This reaction is catalyzed by 5'-deiodinase which occurs in abundance in the liver and kidney, but some deiodination occurs in most other tissues. There are two types of 5'-deiodinase (types I and II). Type I is the predominant form in the liver, kidney and thyroid, and deiodinates in the following order: rT₃ > T₄ > T₃. Type II is the predominant deiodinating enzyme in the brain, pituitary and skin and deiodinates T₄ > rT₃. Most T₃ (~80%) is produced by extrathyroidal deiodination of T₄ and the rest by the thyroid gland. Total T₃ production is 30 to 40 μg per day. Its degradation, mostly by deiodination, is much more rapid than that of T₄, reaching about 75% each day. The production rate of rT₃ is 30 to 40 μg per day, nearly all of which is extrathyroidal. Degradation of rT₃ is mostly by deiodination, and is even more rapid than that of T₃.

Ingested iodine is rapidly absorbed and distributed in the extracellular iodine pool, which it leaves via transport into the thyroid gland or by renal excretion. Expansion of the extracellular iodine pool is caused by iodine-containing drugs such as amiodarone or radiographic contrast materials such as Telepaque[®] or Oragrafin[®]. When this occurs, administered I-131 is so diluted within the expanded iodine pool that only a small fraction of I-131 is captured by the thyroid. This is why it is necessary to measure urine iodine levels when there is any question that a patient being prepared for I-131 therapy may have been exposed to pharmacologic doses of iodine. It also underscores

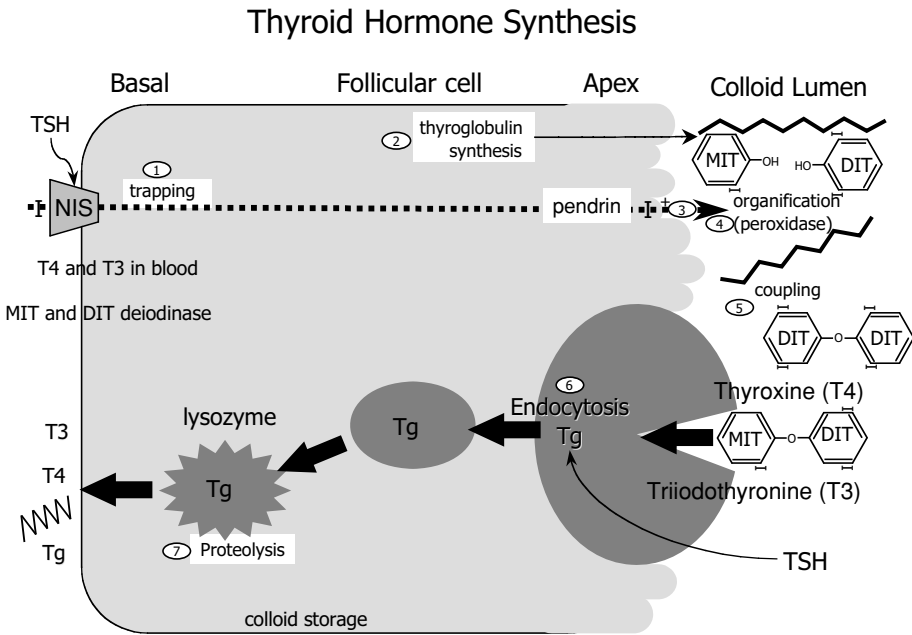


Figure 3. Thyroid hormone synthesis. Thyroid hormones are synthesized in the thyroid gland via the following steps: (1) thyroid iodide transport (trapping), a TSH-stimulated process mediated by sodium-iodide symporters at the basolateral membranes of the cell; (2) synthesis of thyroglobulin, a 660 kilodalton protein composed of two non-covalently linked subunits that contain tyrosyl residues; thyroglobulin is synthesized and glycosylated in the rough endoplasmic reticulum and then incorporated into the exocytotic vesicles that fuse with the apical cell membrane, only then are tyrosine residues iodinated; (3) iodide is transported by pendrin, a membrane iodide-chloride transporter, to exocytotic vesicles fused with the apical cell membrane; (4) oxidation of iodine is catalyzed by thyroid peroxidase, which produces iodination (organification) of about 10% of the tyrosine residues in thyroglobulin; (5) coupling of tyrosine residues produces T_4 by coupling two diiodotyrosine residues and T_3 by coupling one monoiodotyrosine and one diiodotyrosine within a thyroglobulin molecule; coupling is not a random process, instead T_4 and T_3 are formed at regions of the thyroglobulin molecule with unique amino acid sequences; (6) to liberate T_4 and T_3 , thyroglobulin is reabsorbed into the thyroid follicular cells in the form of colloid droplets (endocytosis); (7) the colloid droplets fuse with lysosomes in which thyroglobulin is hydrolyzed to T_4 , T_3 and the thyroid hormones and about 100 μg of thyroglobulin is released from the thyroid each day, a tiny fraction of the 25 mg that must be hydrolyzed to yield the 100 μg of T_4 that is secreted each day.

the necessity of a two-week low iodine-diet in preparation for I-131 therapy, even in patients who have not been exposed to iodine-containing drugs.

THYROIDAL IODINE TRANSPORT

Iodine is transported into thyroid follicular cells against an electrochemical gradient (Fig. 3). Its transmembrane transport is linked to that of sodium, and is energy-dependent and saturable, and requires oxidative metabolism. It is transported via the sodium-iodide symporter (NIS), a transmembrane protein located in the basolateral membrane of

follicular cells, which responds to thyrotropin stimulation (thyroid stimulating hormone, TSH) (Smanik 1996). Functional NIS is also present in the malignant follicular cells of papillary, follicular and Hürthle cell cancers that concentrate I-131 after intense TSH stimulation (Shen 2001). In some thyroid cancers, however, NIS is not responsive to TSH, or is absent, which causes them not to take up I-131. NIS is also present in a variety of nonthyroidal tissues such as the parotid glands, breast tissues, gastric mucosa and nasolacrimal ducts, explaining why they may sustain injury from I-131 therapy.

A phenomenon termed the Wolff–Chaikoff effect is an acute decrease in thyroid hormone production and release that occurs when large amounts of iodine accumulate in the thyroid follicular cell in response to the administration of pharmacologic doses of iodine. However, after about 2 days there is an adaptation to this effect that spontaneously decreases the transport of iodine into the follicular cell, even in the presence of continued high plasma iodide concentrations. This lowers intrathyroidal iodine concentration below a critical inhibitory threshold thus allowing thyroid hormone synthesis and secretion to resume. Escape from the Wolff–Chaikoff effect is caused by an iodine-induced decrease in NIS that blocks iodide transport into the follicular cell (Eng 1999).

THYROID HORMONE SYNTHESIS, STORAGE AND RELEASE

Iodine, after entering into and rapidly diffusing through the thyroid follicular cell, is transported through the apical membrane of the cell by pendrin, a membrane-bound iodide–chloride transporter (Fig. 3). It is here that the first process of thyroid hormone synthesis begins with the rapid oxidation of iodine to iodide molecules that then bind to tyrosyl residues (organification) of thyroglobulin, a 660 kilodalton glycoprotein synthesized by follicle cells (Van Herle 1979). Iodinated thyroglobulin rapidly moves into intra-luminal colloid stores, becoming their main component. Thyroid hormones (T_3 and T_4) are synthesized by the coupling of iodinated tyrosine molecules and remain attached to the thyroglobulin stored in colloid until leaving the gland. Under normal circumstances the thyroid gland stores enough thyroid hormone to maintain T_3 and T_4 within physiologic levels for about 2 weeks. Thus, serum thyroid hormone levels fall over several weeks after total thyroidectomy has been performed for differentiated thyroid carcinoma.

In response to TSH stimulation, colloid droplets are taken from the lumen into the follicular cell by a process termed endocytosis in which they are hydrolyzed, releasing into the circulation each day about 80 to 100 μg of T_4 and only a small amount ($\sim 10 \mu\text{g}$) of T_3 , along with about 100 μg of thyroglobulin. This process also occurs to some extent in differentiated malignant follicular cells, thus providing a unique means of monitoring a patient's status postoperatively by measuring serum thyroglobulin (Tg) levels (Van Herle 1975).

The process of thyroid hormone synthesis and secretion is regulated by a feedback loop in which thyrotropin-releasing hormone (TRH) increases the secretion of TSH, which stimulates the synthesis and secretion of T_3 and T_4 by the thyroid gland, and both hormones in turn inhibit TRH release and TSH secretion (Fig. 4).

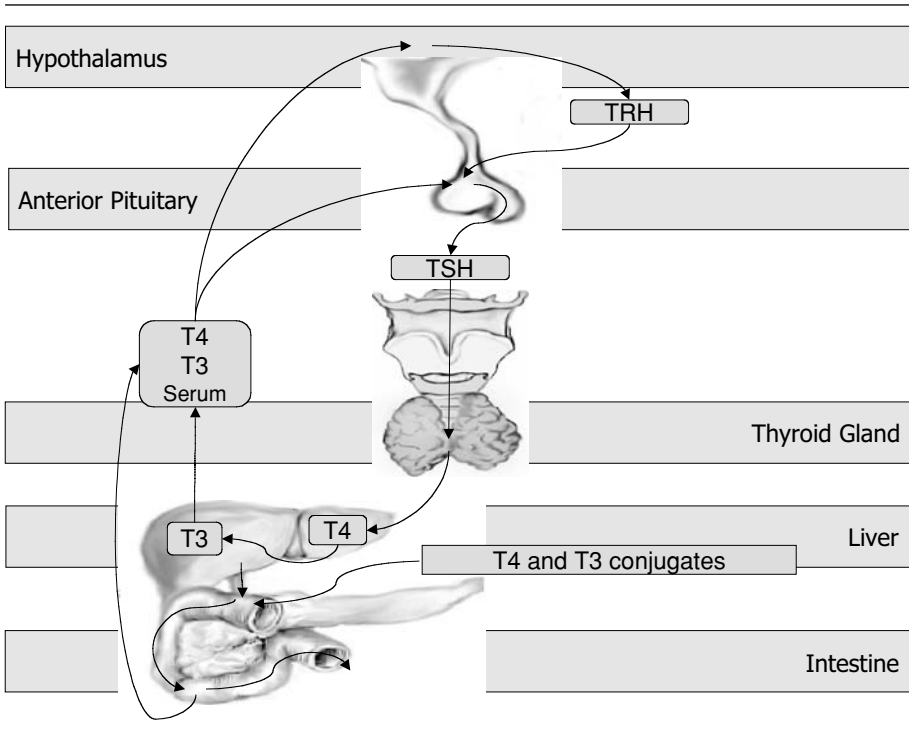


Figure 4. Regulation of thyroid hormone synthesis and secretion. Feedback loops regulate the synthesis and secretion of thyroid hormones (thyroxine [T4] and triiodothyronine [T3]). Regulation of thyroid secretion involves signals from the hypothalamus (thyrotropin-releasing hormone [TRH]) which in turn regulates the secretion of thyrotropin (thyroid stimulating hormone, [TSH]). Thyroidal synthesis and secretion of thyroid hormone is regulated by TSH. Type I deiodinase converts T4 to T3, and also converts T3 to reverse T3. The liver deiodinases converts T4 to T3 and then to mono- and diiodotyrosine.

Once released into the blood, 99.95% of T4 and 99.5% of T3 are bound to several serum proteins, termed thyroxine-binding globulin (TBG), transthyretin (TTR, formerly termed thyroxine-binding prealbumin) albumin and lipoproteins. Thyroid hormone bound to these proteins is in equilibrium with the unbound (free) thyroid hormone—the biologically active component of circulating T4 and T3 (Engler 1984). The serum half-life of T3 and T4 is determined by their binding affinities to carrier proteins. The T3-carrier protein bond is relatively weak, resulting in a short serum half-life of about 12 hours, whereas T4 is bound more tightly and thus has a longer serum half-life of about 7 days. This is why T3 is often substituted for T4 before withdrawing thyroid hormone for I-131 therapy.

Most (~80%) T4 is converted to T3 in the liver and many other tissues by the action of T4 monodeiodinases, while the rest is conjugated with sulfate and glucuronide in the liver, excreted in the bile and partially hydrolyzed in the bowel (Fig. 4). This is why diffuse hepatic uptake of I-131 is seen on a whole body scan when radiolabeled T4 is

released into the circulation from normal thyroid tissues or differentiated thyroid cancers that have taken up and been treated by I-131.

Thyroid hormone, mainly in the form of T₃, has critical actions on virtually all cells in the body; however, there are especially important effects of thyroid hormone on the heart and bone that occur with deliberate levothyroxine over-treatment, which can cause serious loss of bone mineral density in post-menopausal women, and atrial fibrillation and measurable cardiac dysfunction in both sexes.

CALCITONIN

Calcitonin is a 32-amino acid polypeptide. In pharmacologic doses it inhibits osteoclastic bone resorption, but the physiologic role of calcitonin is minimal in the adult skeleton where its effects are transient, probably because of calcitonin receptor downregulation. The effects of calcitonin deficiency are unknown, mainly because studies have been unable to separate the effects of calcitonin deficiency from hypothyroidism. Calcitonin is produced by, and is the main tumor marker for, medullary thyroid carcinoma (Machens 2005). Tumor secretion of calcitonin that occurs in medullary thyroid carcinoma may cause diarrhea or facial flushing in patients with advanced tumor stage.

PARATHYROID HORMONE (PTH)

PTH is one of two major hormones controlling calcium and phosphate metabolism. Its secretion is regulated by serum ionized calcium acting via an exquisitely sensitive calcium-sensing receptor on the surface of the parathyroid cells. Within seconds of the induction of hypocalcemia, PTH is released as the biologically active form of the hormone, an 84-amino acid polypeptide with a 2 to 4 minute half-life in plasma. The immediate effect of PTH is to rapidly mobilize the readily available skeletal stores of calcium that are in equilibrium with the extracellular fluid (Felsenfeld 1999). Later, it stimulates the release of calcium (and phosphate) by activating bone reabsorption. PTH thus maintains ionized serum calcium concentrations within a narrow range. The hormone also stimulates renal tubular calcium reabsorption and inhibits renal tubular phosphate reabsorption, thereby further raising both the serum calcium and phosphate concentrations.

VITAMIN D

The other major hormonal control of calcium and phosphate metabolism is mediated by vitamin D, a fat soluble vitamin that is readily absorbed from the intestine or synthesized in the skin in response to ultraviolet light. Vitamin D travels to the liver where it, and endogenously synthesized vitamin D₃, are metabolized to 25-hydroxyvitamin D (calcidiol) (Compston 2000). PTH and hypophosphatemia both stimulate the renal enzyme 1,α-hydroxylase, which converts calcidiol to 1,25-dihydrovitamin D (calcitriol, Rocaltrol[®]), a form of vitamin D that is 100-fold more potent than its precursor. The most important biological action of calcitriol is to promote intestinal calcium absorption. These physiologic responses to hypocalcemia explain why calcium replacement alone is insufficient therapy for hypoparathyroidism: calcitriol synthesis is impaired by the

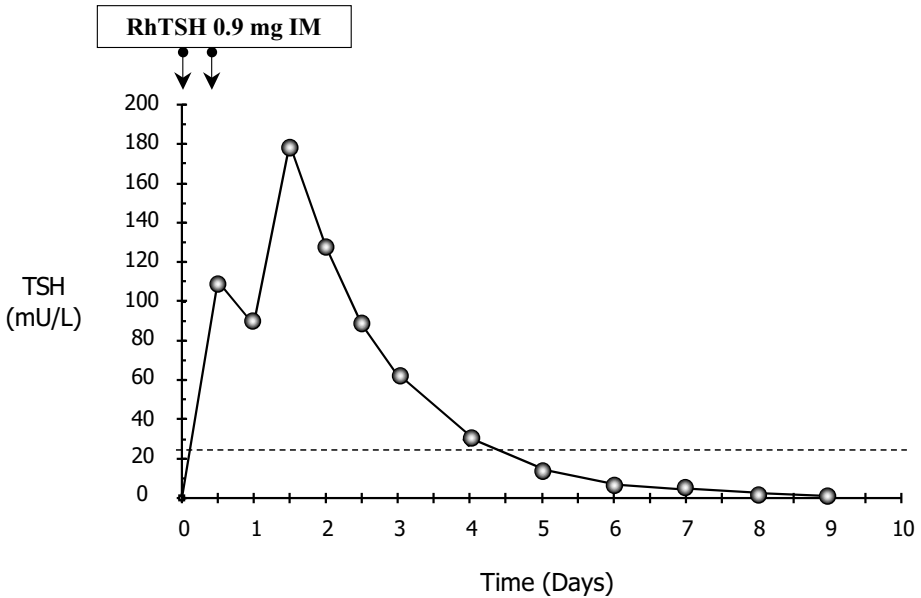


Figure 5. Serum TSH levels after two injections of recombinant human TSH-alpha (Thyrogen[®]) used to stimulate I-131 uptake and serum thyroglobulin levels. Fig. supplied by the Genzyme Corporation Cambridge, Massachusetts, U.S.A.

low serum PTH levels and oral calcium is simply not sufficiently absorbed without calcitriol.

PHARMACEUTICAL NAMES OF TSH, T3 AND T4 AND VITAMIN D PREPARATIONS

To practitioners that do not routinely manage patients with thyroid disease, it is useful to have a reference that lists the commercial trade names of TSH, T3 and T4:

- **Thyrotropin (TSH):** Recombinant Human Thyroid Stimulating Hormone (rhTSH) THYROGEN[®]
 - **Activity and pharmacodynamics:** TSH levels peak about 3 to 24 hours after injection, with a serum half-life of about 24 hours (Fig. 5). This varies according to the patient's body weight. It is not necessary to measure serum TSH levels after Thyrogen[®] injection.
 - **Thyroid cancer in adults:** Usual adult dose is 0.9 mg IM on two consecutive days, 24 hours apart.
 - For radioiodine imaging or use with FDG-PET scanning the isotope should be given 24 hours following the final Thyrogen[®] injection.
 - For serum Tg testing, serum levels should be obtained 72 hours after the final injection of Thyrogen.[®]

- **Thyroid Cancer in Children:** The drug may be used in children >16 years of age in the same doses as given to adults.
- **ADVERSE REACTIONS:**
 - **Minor:** The most common reaction is mild headache, which can occur in up to 10% of patients. A few patients develop fever, chills dizziness, nausea, and vomiting or muscle weakness, or a flu-like syndrome.
 - **Significant:** Edema or enlargement of tumor that can cause acute compression symptoms in the central nervous system, neck or elsewhere, resulting in respiratory distress, stridor or neurological symptoms. This has generally occurred in patients with known residual tumor.
- **Liothyronine (T3)** (triiodothyronine): CYTOMEL[®] TRIOSTAT[®]
 - **Hypothyroid adult under age 50 years without cardiac disease:** starting oral dose 25 mcg/day; increase by 12.5 mcg/day increments every 1–2 weeks to a maximum of 100 mcg. Usual maintenance dose is about 1 mcg/kg/day or 75 to 100 mcg/day.
 - **TSH suppressive dose in adults under age 50 years without heart disease:** 75 to 100 mcg/day for 7 to 14 days.
 - **TSH suppressive dose in adults over age 50 years or anyone with heart disease:** 5 mcg/day increasing by 5 mcg every two weeks.
 - **ADVERSE REACTIONS:** There are significant (1% to 10%) adverse cardiovascular reactions to this drug, including arrhythmias, tachycardia, myocardial infarctions, syncope, heart failure and sudden death.
- **Levothyroxine (T4):** SYNTHROID[®], LEVOXYL[®], NOVOTHYROX[®], UNITHROID[®] Generic Products are also available.
 - **Hypothyroidism:** The usual oral dose is 1.7 mcg/kg/day in otherwise healthy adults under age 50 years and children in whom growth and puberty are complete. The dose should be titrated every 6 weeks until the target TSH is achieved. The average starting dose is ~100 mcg.
 - **Hypothyroid adults over age 50 years or anyone with cardiac disease:** Initial dose is 25 to 50 mcg/day, adjusted by 12.5 to 25 mcg increments at 4–6 week intervals.
 - **TSH suppression with well differentiated thyroid cancer:** Highly individualized, but some patients require doses >2 mcg/dg/day to suppress TSH <0.1 mIU/L.
 - **Pregnancy:** In women taking levothyroxine prior to pregnancy, the dose of levothyroxine increases about 30% immediately after conception (Alexander 2004).
 - **Absorption:** Decreased by iron tablets or vitamins containing iron, aluminum- and magnesium-containing antacids, calcium carbonate, simethicone, sucralfate, raloxifene, cholestyramine, colestipol, Kayexalate[®] (Siraj 2003).
 - **Factors altering dosage:** Should be taken on an empty stomach at least 30 minutes before food. Simultaneous food intake lowers absorption, estrogens require increased levothyroxine dosage.
 - **Using different levothyroxine preparations:** Levothyroxine has a narrow therapeutic index. Products inappropriately deemed bioequivalent may put patients at

risk for iatrogenic hyperthyroidism or hypothyroidism. Thus, it is imperative that the patient remain on the same brand of thyroid hormone as initially prescribed because there may be important differences in TSH levels in patients receiving the same doses of different brands of levothyroxine.

- **Calcitriol (Vitamin D):** Rocaltrol[®] 0.25 mcg or 0.5 mcg tablets; Calcijex[®]; injection 1 mcg/1ml.
 - **Hypoparathyroidism in adults:** Oral dosage is individualized to maintain serum calcium levels of 9–10-mg/dL, which usually requires 0.5 to 2 mcg a day. Serum calcium levels must be monitored frequently until the patient has reached a stable dosage. Adequate daily calcium intake is necessary to maintain target serum calcium levels.
 - **Acute Hypocalcemia:** Patients may develop muscle cramps, circumoral or limb paresthesias, carpopedal spasm or laryngospasm, generalized or focal seizures, or hypotension. Chvostek's or Trousseau's signs are positive.
 - **Chvostek's sign** is elicited by tapping in the pretragal area and watching for an involuntary twitch of the lips. Up to 10% of patients who are normocalcemic will have a positive Chvostek's test.
 - **Trousseau's sign** is performed by occluding the brachial artery with a blood pressure cuff for 3 minutes. A positive test is carpopedal spasm.
 - Tetany is uncommon unless the serum ionized calcium concentration is less than 2.8 mg/dL.
 - Therapy is with intravenous calcium. Calcium should be diluted in dextrose and water or saline, because concentrated calcium solutions are irritating to veins. Calcium gluconate is preferred because calcium chloride may cause tissue necrosis.
 - **Calcium gluconate** is given intravenously 2–15 g/24 hours as a diluted solution.
 - **Major side effects:** Hypercalcemia with attendant symptoms of polyuria, polydipsia, fatigue, mood changes, altered consciousness and hypotension.
 - **Drug interactions:** Cholestyramine, colestipol may decrease absorption and the effects of Calcitriol; corticosteroids may decrease hypercalcemic effect of Calcitriol.

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<http://www.springer.com/978-0-387-25713-6>

Essentials of Thyroid Cancer Management

Mazzaferri, E.L.; c/o Jessica Kirwan, R.J.A. (Eds.)

2005, XVIII, 462 p., Softcover

ISBN: 978-0-387-25713-6